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Research Communication

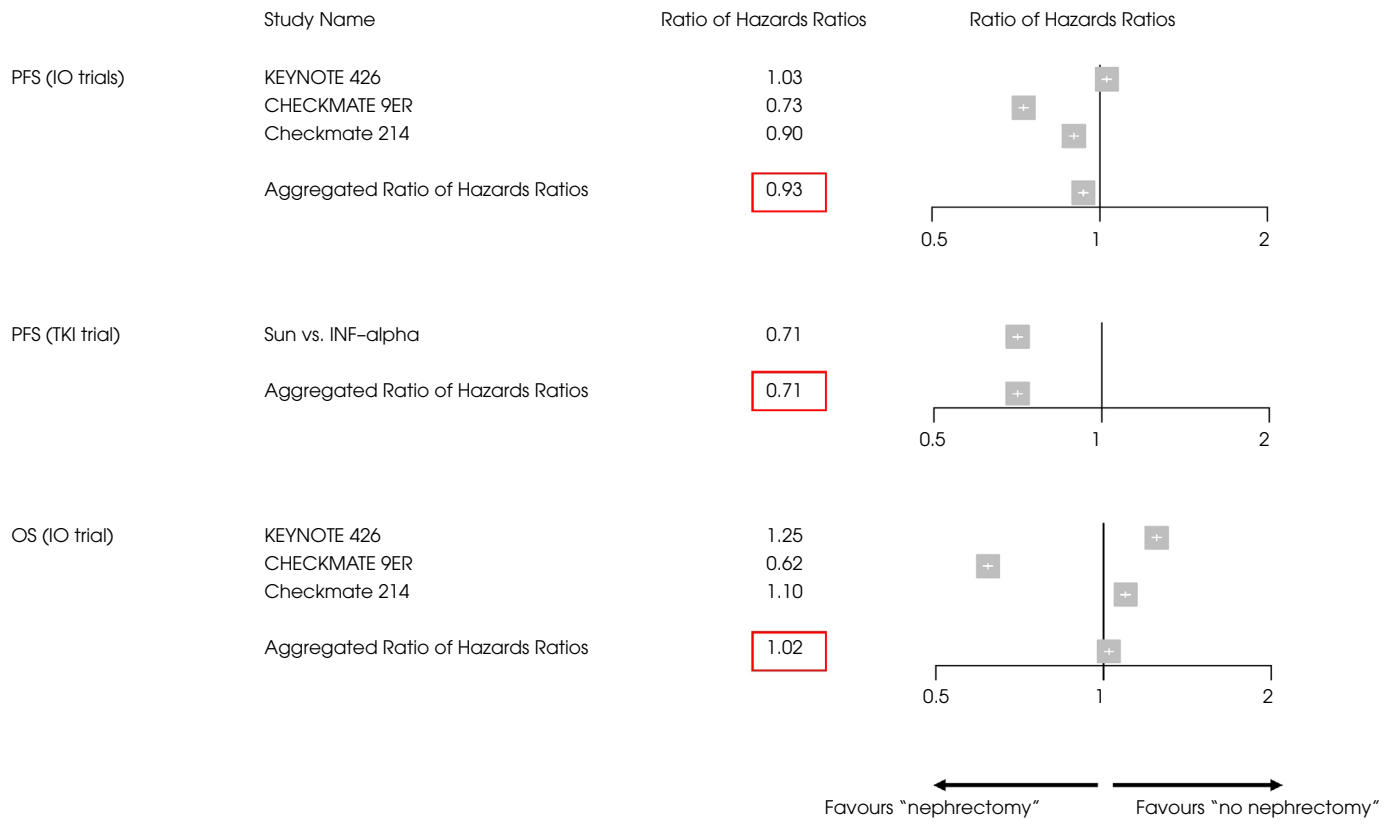
The role of nephrectomy in metastatic renal cell carcinoma in the immuno-oncology era

Three first-line, randomised phase III trials (Checkmate 214 [1], Checkmate 9ER [2], and Keynote 426 [3]) relied on predefined statistical criteria to validate the survival advantage of immuno-oncology (IO)-based systemic treatment in metastatic RCC (mRCC) relative to sunitinib. Within each of these three trials, stratification according to prior nephrectomy was addressed in *post hoc* progression-free survival (PFS) and overall survival (OS) analyses. We focussed on these three *post hoc* analyses in addition to illustrating the effect of prior nephrectomy in the pivotal sunitinib vs interferon trial (Motzer *et al.* [4]) for comparison purpose [1–4].

The rates of prior nephrectomy varied across trials. In Keynote 426, the prior nephrectomy rate was 83% (treatment-arm, pembrolizumab/axitinib) vs 84% (control-arm, sunitinib) [3]. In Checkmate 9ER, prior nephrectomy rate was 69% (treatment-arm, nivolumab/cabozantinib) vs 41.5% (control-arm, sunitinib) [2]. In Checkmate 214, prior nephrectomy rate was 82% (treatment-arm, nivolumab/ipilimumab) vs 80% (control-arm, sunitinib) [1].

The proportions of favourable-, intermediate- and poor-risk patients also varied across trials. In the prior nephrectomy cohort of Keynote 426, the proportions of intermediate- or poor-risk patients ranged from 63.5% (treatment-arm) to 64% (control-arm) [3]. In the cohort of Keynote 426 without prior nephrectomy, the proportions of intermediate- or poor-risk patients were even higher (90% in the treatment arm and 96% in the control-arm) [3]. In Checkmate 214 and Checkmate 9ER, no detailed information on risk proportions according to nephrectomy status was available [1,2]. In Checkmate 9ER, across cohorts with and without prior nephrectomy, proportions of intermediate- or poor-risk

Fig. 1 Forest plots displaying the association of prior nephrectomy on PFS and OS in mRCC in three first-line IO trials and one trial from the tyrosine kinase inhibitor (TKI) era for comparison.



patients were 77% (treatment) vs 78% (control) [2]. In Checkmate 214, across cohorts with and without prior nephrectomy, proportions of intermediate- or poor-risk patients were 77% and 77%, respectively [1].

Regarding PFS, prior nephrectomy status was associated with longer PFS in Checkmate 9ER [2] (ratio of hazards ratios [rHR] 0.73) and Checkmate 214 [1] (HR 0.90), but not in Keynote 426 [3] (HR 1.03). For comparison, in the pivotal sunitinib vs interferon trial, prior nephrectomy status was also associated with longer PFS (HR 0.71) [4]. Regarding OS, prior nephrectomy status was associated with longer OS only in Checkmate 9ER [2], but not in Checkmate 214 [1] or in Keynote 426 [3] (Fig. 1).

The above observations suggest more favourable PFS in prior nephrectomy patients in two of the three IO trials. Lack of PFS benefit in Keynote 426 [3] may be related to high proportion of intermediate- or poor-risk patients in the prior nephrectomy arm in addition to the smallest proportion of patients without prior nephrectomy of all three trials. Indirectly, the highest proportion of prior nephrectomy patients in Keynote 426 [3] endorses the use of nephrectomy in the setting examined within this trial. Nonetheless, further *post hoc* analyses, especially, those from the CLEAR trial (ClinicalTrials.gov Identifier: NCT02811861) should ideally complement our observations [5]. Finally, our observations should be interpreted in the light of their non-randomised design. Therefore, the beneficial effect of prior nephrectomy on PFS should be interpreted as a mere association and not causation. Furthermore, it should also be emphasised that prior nephrectomy status indicates the use of nephrectomy at non-metastatic stage in most patients. Consequently, it cannot be interpreted as synonymous with cytoreductive nephrectomy. Nevertheless, even after taking into account these considerations, it appears likely that the role of nephrectomy in the management of mRCC will persist also in the era of IO treatment. However, ideal patient selection and timing of nephrectomy in patients with mRCC treated with IO regimens is currently unclear. In this regard, future guideline recommendations on the role of nephrectomy in the IO era will eventually be shaped by the results of several ongoing prospective randomised trials (NCT03055013, NCT02210117, NCT03288532, NCT03138512, NCT03142334, NCT03024996).

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Disclosure of Interests

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Abbreviations: IO, immuno-oncology; mRCC, metastatic RCC; OS, overall survival; PFS, progression-free survival; rHR, ratio of hazards ratios.